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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/216,641	12/17/98	BURKOTH T	7010-0001

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EXAMINER	
NGUYEN, Q	
ART UNIT	PAPER NUMBER
1632	7

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Please find below and/or attached an Office communication concerning this application or pr ceeding.

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Office Action Summary	Application No. 09/216,641	Applicant(s) BURKOTH ET AL.	
	Examiner Quang Nguyen	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's response to the Restriction Requirement, dated 05 October 2000, in paper no. 7 is acknowledged. Applicant elected the claims of Group II, claims 15-40, without traverse.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Great Britain on 11 June 1996 and 11 September 1996. It is noted, however, that applicant has not filed certified copies of the above applications as required by 35 U.S.C. 119(b). It is further noted that applicant has also not filed certified copies of PCT/GB97/01636 and PCT/GB97/02478 as required by 35 U.S.C. 365(c).

Specification

The disclosure is objected to because of the following informalities: The brief description of the Figures is not adequate for explaining abbreviations in the Figures, particularly Fig. 2. For example, What does B/P or F#2 or F#3 or TCC or THC stand for? Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-37, 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 15-28 are drawn to a method for forming densified particles from a particulate pharmaceutical preparation, comprising compacting the preparation to provide a compacted pharmaceutical preparation and size-reducing the compacted preparation into densified particles of suitable size and density for transdermal delivery thereof by needleless injection. Claims 29-37 are directed to a composition of a densified particulate pharmaceutical composition formed from a lyophilized or spray-dried pharmaceutical composition preparation, said densified composition having an average particle size in the range of about 0.1 to 250 μm mean diameter and a particle density in the range of 0.1 to 25 g/cm^3, whereas claim 39 is directed to a unit-dosage container for a needless syringe comprising the same composition. Claim 40 is directed to a method of delivering a selected pharmaceutical agent to a vertebrate subject, said

method comprising providing the same compacted particulate pharmaceutical preparation and delivering to a target tissue or cell of the vertebrate subject by needleless syringe.

With regard to the nature of the instant claims, the specification discloses compositions comprising pGREEN-1 or a human growth hormone (hGH) or β-galactosidase expression vector plasmid with trehalose sugar excipient, which were compressed, ground and sieved to form condensed nucleic acid compositions. The compositions were individually administered through a needleless injection device to target skin surfaces of either C57BL/10 mice or female pigs. After 24 hours of administration, biopsy samples revealed GFP and β-galactosidase expression in treated sites, whereas hGH expression was not detected. The lack of hGH expression was attributed to the low loading density of the nucleic acid in the composition (See example 2). The specification further teaches the preparation of a densified composition comprising lyophilized recombinant hGH powder (Genotropin), and it demonstrates that in comparison with the lyophilized rhGH powder, a higher proportion of the densified composition penetrated porcine skin by needleless injection. Additionally, the specification teaches that markedly increased blood serum levels of rhGH were obtained in New Zealand White rabbits that were intradermally administered with densified Genotropin particles through the needleless injection system.

The above evidence is noted and considered. However the evidence can not be extrapolated to the instant claimed invention which when read in light of the specification is drawn to a densified particulate pharmaceutical composition comprising

a gene construct or a peptide/protein, a method for preparing the same, and a method of delivering the same predominantly for the purposes of gene therapy and genetic immunization (See pages 22-24 of the specification). As enablement requires the specification to teach how to make and **use** the claimed invention, the instant specification fails to enable the use of the densified particulate pharmaceutical composition, and methods of preparing and delivering the same for gene therapy and genetic immunization.

Regarding to the gene therapy aspect of the claims, the specification is not enabled for the claimed invention because at the effective filing date of the present application, gene therapy was considered to be immature and highly unpredictable. The specification fails to provide guidance or direction for one skilled in the art to administer the compacted or densified particulate pharmaceutical composition of the present invention into a vertebrate subject through a needleless injection system, such that the expression of a DNA sequence encoding a therapeutic protein/peptide in target cells or tissues of the subject is at sufficient levels to yield therapeutic effects. There is no specific guidance as to promoters, vectors, dosage regime that is deployed to treat a plethora of diseases, disorders and genetic defects such as, AIDS, cancer, neurological diseases, cardiovascular diseases, cystic fibrosis, adenosine deaminase deficiency among many others as contemplated by the instant claimed invention. Furthermore, there is no correlation between the expression of green fluorescent protein (GFP) or β-galactosidase or a transient elevated blood serum level of recombinant hGF with the expected desired therapeutic results for the treatment of aforementioned diseases,

disorders and genetic defects. As the art does not teach such a correlation nor provide such guidance, it is incumbent upon the specification to do so. Given the lack of guidance or direction provided by the instant specification, it would have required undue experimentation without a predictable expectation of success for one skilled in the art to make and **use** the claimed invention.

It has been noted that there are several factors limiting an effective gene therapy, and these include sub-optimal vectors, the lack of long-term and stable gene expression, and most importantly the efficient gene delivery to target tissues. The specification fails to provide teachings showing that a gene construct in the densified particulate pharmaceutical composition of the instant invention could provide an efficient therapeutic transgene expression in targeted cells or tissues that results in desired treatment outcomes for any and all diseases contemplated by the present application. Available gene delivery systems have recently been reviewed by Wivel & Wilson (Methods of gene delivery, Hematol. Oncol. Clin. North Am. 12:483-501, 1998). In a summary, Wivel and Wilson stated that "One of the major challenges still confronting the field is the design of more efficient vectors. The gene delivery systems being used today will undoubtedly be seen as crude when compared with future developments. It is unlikely that there will ever be a universal vector, but rather there will be multiple vectors specifically designed for certain organ sites and certain diseases.....It will be necessary to do much more fundamental research in cell biology, virology, immunology, and pathophysiology before vectors can be significantly improved." (pages 498-499 in Summary section).

The specification fails to address issues such as the fate of delivering recombinant gene transfer vectors, the fraction of vectors taken up by targeted cells, the level of mRNA produced, the stability of the recombinant protein produced, the recombinant protein's compartmentalization and its bioactive activity. These factors differ dramatically based on which recombinant protein being produced, and the desired therapeutic effect being sought. Therefore, the level of gene expression, its duration and its *in vivo* therapeutic effects are not always predictable, and hence they can not be overcome by routine experimentation. With the lack of guidance and direction provided by the specification, it would have required undue experimentation without a predictable expectation of success for a skilled artisan to make and **use** the instant invention.

Regarding to the deliverance of a compacted particulate pharmaceutical preparation to a target tissue or cell of a vertebrate subject through a needleless syringe, the specification fails to provide sufficient guidance or teachings on vector targeting to specific tissues or cells in the subject. At the effective filing, vector targeting *in vivo* to desired tissues, organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated

that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). The specification fails to provide sufficient guidance for a skilled artisan to overcome the unpredictability of vector targeting, such that efficient gene transfer and expression is achieved in specific target tissues or cells through a needleless syringe system in order to attain desired therapeutic results.

With regard to the nucleic acid immunization aspect of the instant claims, the state of the art is new and unpredictable at the effective filing date of the present application. Chattergoon et al. (FASEB J. 11:753-763, 1997) stated that "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology

is considered an emerging technology" (column 1, paragraph 2, page 762) and "There is little evidence that the immune response induced by these vaccines will be completely protective against any human pathogen" (page 762, paragraph bridging columns 1-2). Most recently, Leitner et al. (Vaccine 18:765-777, 2000) further stated that "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Leitner et al. also listed several variable factors affecting the immunogenicity of genetic vaccines. These include: the structure of the plasmid backbone, amount of plasmid delivered, expression levels of the antigen, age and strain of the particular species, target tissue, and route of immunization among others (See Table 1, page 767). It is recognized that the animal model should correlate to the disease conditions studied. It is impossible to predict whether an untested antigen of an infectious pathogen will elicit a protective immune response in a given type of animal and the route of administration was recognized as being a critical parameter determining whether protective immunity is elicited. Since the scope of claim 40 encompasses any and all vertebrate subject, one skilled in the art has also recognized that results observed in animal model system following testing of a DNA expression vector-based agent are not predictive of outcome or efficacy in applications in other species of animal or in humans, due to differences in anatomy, cell biology, genetics, and immunology between different types of animals and between the animal models and humans. This is further supported by the teachings of McCluskie et al. (Mol. Med. 5:287-300, 1999) who stated that "it is probably safe to say that any vaccine

that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors." (column 2, last paragraph, page 296). The instant specification fails to provide guidance or direction demonstrating that the claimed method of delivering a selected pharmaceutical agent in the form of a compacted particulate pharmaceutical preparation is effective for nucleic acid immunization purpose in any and all vertebrate subjects.

With respect to the use of a densified pharmaceutical composition comprising a protein or peptide for therapeutic purposes, the instant specification fails to provide guidance demonstrating that desired therapeutic results can be attained with said densified pharmaceutical composition through the needleless syringe system. The specification fails to address similar issues raised in the preceding paragraphs, for example, obstacles encountered in the establishment of a stable and effective levels of therapeutic protein or peptide in specific cells or tissues in any and all vertebrate subjects, such that desired therapeutic outcomes can be achieved. Additionally, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictablity of factors involved.

Accordingly, due to the lack of guidance and direction provided by the specification, the unpredictability and current state of the gene therapy and nucleic acid immunization and physiological arts, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and **use** the instantly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claims 24 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 24, the term "and/or" is unclear and therefore renders the claim indefinite. Does the method involve milling or sieving separately or both? Clarification is needed.

Claim 40 is indefinite because the claim is dependent on itself. For the purpose of compact prosecution, it is presumed that the pharmaceutical preparation that claim 40 refers to is that according to claim 37.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 38 is rejected under 35 U.S.C. 102(b) as being anticipated by Sanford et al. (U.S. Patent No. 5,100,792).

The claim is directed to particles of a suitable size and density for transdermal delivery by needless injection, consisting of a gene construct and a pharmaceutically acceptable excipient.

It should be noted that for composition claims, an intended use limitation is not given any patentable weight. Sanford et al. disclosed the making of inert particles including gold, tungsten or other metal spheres (pharmaceutically acceptable excipient) coated with nucleic acids such as DNA or RNA of the appropriate size and density to be propelled at cells at a speed whereby the particles penetrate the surface of the cells and become incorporated into the interior of the cells (See column 6, lines 44-49; column 7, lines 13-18). Therefore, the reference clearly anticipates the claimed invention.

Conclusions

Claims 1-37 and 39-40 are free of prior art. At the time of the instant invention, the prior art did not teach or fairly suggest a densified or compacted particulate pharmaceutical composition, a method for preparing the same, and the method of delivering the same to a vertebrate subject.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Deborah Crouch, Ph.D., may be reached at (703) 308-1126, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Deborah Crouch

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PRIMARY EXAMINER
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Quang Nguyen, Ph.D.
12/11/2000